REMARKS

Claims 1-20 are pending. Claims 1, 2, 4-8, 11 and 12 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Platz et al, U.S. Patent 5,418,130. Claims 1-17 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Platz et al, U.S. Patent 5,418,130. Claims 1-20 are rejected under obviousness-type double patenting as being unpatentable over claims 20-35 of U.S. Patent 6,093,725 in view of U.S. Patent 5,418,130.

Rejection under 35 U.S.C. § 102 (b)

Claims 1, 2, 4-8, 11 and 12 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Platz et al, U.S. Patent 5,418,130. Applicants' pending claims are to a method of treating red blood cells using a pathogen inactivating compound having a functional group that is electrophilic, wherein the electrophilic group can react covalently with the nucleic acid. The method further includes the use of a quencher comprising a nucleophilic group that can react covalently with the electrophilic group of the pathogen inactivating compound.

Applicants provide a brief summary of their invention to help understand the distinction from the Platz reference. The pathogen inactivation involves the use of compounds that are targeted to nucleic acids and then react by covalently binding to the targeted nucleic acid. This covalent binding occurs through the reaction of an electrophilic group (e.g. a mustard group) of Applicants' compounds with a nucleophilic group on the nucleic acid. This process does not involve the generation of reactive oxygen or free radical species. A quencher is added in order to reduce the reactivity of the pathogen inactivating compound that is not associated with the nucleic acid. A suitable nucleophilic group, such as the sulfur atom of glutathione, is used to react with the electrophilic group to prevent unwanted side reactions. Applicants submit a declaration by Dr. Wollowitz indicating that this quenching is unrelated to glutathione quenching of reactive oxygen or free radical species.

> " The quenching of electrophiles by glutathione as it applies to Applicant's invention is neither described nor implied by Platz. Glutathione, and thiols in general, are known to react with electrophiles by a different mechanism than they react with singlet oxygen or reactive oxidative species. For example, the reaction of nucleophilic glutathione with electrophilic nucleic acid alkylators to protect cells occurs by a process in which the thiol group (RS-) covalently reacts with the alkylator [see, e.g. Bolton et al., Drug Metabolism

> and Disposition 21(6): 986-996, 1993]. The reaction of glutathione with singlet oxygen, other highly reactive oxygen species or free radicals involves the donation of an electron and/or a hydrogen atom to "quench" the reactive species, resulting in the formation of a thiol radical (RS·) which can then dimerize, be oxidized further or pull a hydrogen off another thiol in the medium. There is nothing in the disclosure of Platz to suggest that the reactivity of glutathione with an electrophilic nucleic acid alkylator is envisioned." (Wollowitz declaration item 6)

Applicants maintain that this invention is not disclosed by Platz, and the declaration by Dr. Wollowitz supports this distinction. While the Office Action correctly states that Platz teaches the covalent reaction of psoralens to nucleic acids, this well known photochemistry is the result of a cycloaddition of a double bond of the psoralen ring structure with a double bond of thymine or uracil in the nucleic acid, as shown in the schematic of columns 27-28 in Platz. This is a general reaction of the psoralen ring and does not involve an electrophilic group. It is understood from the accompanying declaration by Dr. Wollowitz that what the Office Action suggests are electrophilic groups discussed in Platz do not react as electrophiles with nucleic acids according to Applicants' claims.

> "The amine (or phosphine) of Platz, however, without other functional groups attached, is not inherently electrophilic, but is generally nucleophilic. Platz does not indicate any functional groups that might alter the nucleophilic nature of such compounds. A quaternized or protonated amine or phosphine as shown in Platz can interact electrostatically with negatively charged materials but are not known to form covalent bonds. Nor are they known to form an electrophilic group that can react covalently with nucleic acid without transforming the molecule by chemical reactions that would not occur naturally in the biological medium. The groups that are attached to the amine or phosphine indicated in Platz are hydrogen or linear or branched alkyl groups. These groups are not known to induce an amine or phosphine group to become electrophilic and react covalently with nucleic acids. Likewise, the groups that attach the amine or phosphine to the rest of the molecule are not known to induce them to become electrophilic and react covalently with nucleic acids." (Wollowitz declaration item 4)

The purpose of the electrophilic (i.e. cationic) groups discussed in Platz is indicated in column 4, line 27-31:

> "The present invention utilizes a class of compounds based on 3-carboethoxy psoralens, psoralens, angelicins, khellins and coumarins which contain a halogen substituent and a water solubilization moiety, such as, quaternary ammonium ion or phosphonium ion."

The cationic group of Platz is added in order to improve water solubility of the compounds, and is not involved directly in nucleic acid reactivity (Wollowitz declaration item 4, per above). In addition, these preferred compounds of Platz do not react according to the abovementioned psoralen cycloaddition as indicated in column 4, lines 35-39.

> "It is further advantageous in that only one photon of light is required to activate the brominated sensitizer, whereas two photons are required in sequential order of nonbrominated psoralens to complete classical photoadduct DNA cross linking."

This mechanism of the reaction of the preferred psoralens in Platz is detailed in the schematic of columns 29 and 30, indicating that the reaction results in nucleic acid strand cleavage, not covalent addition of the psoralen.

With respect to Applicants' limitation of a quencher, the Office Action indicates that applicant has not demonstrated that the glutathione disclosed by Platz fails to act as recited in Applicants' claims. Applicants see no need to demonstrate this lack of activity when Platz clearly teaches the activity of the glutathione as an antioxidant. Column 26, lines 41-44 states:

> "Antioxidants such as glutathione (an excellent hydrogen atom donor) may be added to the preparation to augment the red cell defenses *against free radical initiated damage.*" [emphasis added]

Further, the glutathione of Platz can not inherently act as recited in the claims, as suggested by the Office Action, since Platz does not disclose an electrophilic group that can react covalently with nucleic acid, as required by the claim.

For the reasons stated above, Applicants feel that the Examiner's interpretation of Platz is misguided. Taken as a whole, Platz teaches psoralen derivatives that react differently than the classic psoralen pathway, i.e. that react by generating free radical damage to the nucleic acid rather than forming a cyclobutane addition to the psoralen ring. While Platz does discuss quenching, including the use of glutathione, the quenchers he refers to are antioxidants used to reduce oxidative damage from compounds that generate free radicals. There is nothing in Platz that suggests the limitations in Applicants' claims relating to an electrophilic group that can react with nucleic acid. Applicants respectfully request that this rejection be withdrawn.

Rejection under 35 U.S.C. § 103 (a) over Platz

Claims 1-17 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Platz et al, U.S. Patent 5,418,130. The Office Action states that Platz discloses a pathogen-inactivating compound having the claimed structure that is quenched using glutathione. As discussed above, Applicants argue that Platz does not disclose a compound with an electrophilic group that can react with nucleic acid. The use of glutathione discussed in Platz was a general reference to its use as an antioxidant with certain psoralen compounds, and is unrelated to quenching per Applicants' claims. In fact, with respect to the preferred compounds discussed in Platz, which contain a cationic group such as a quaternary amine, Platz teaches away from the use of a quencher. Column 6, line 28-48 states:

> "In a preferred embodiment, the sensitizer will bear a charge, preferably a positively charged ammonium or phosphonium group, which can impart water solubility to the sensitizer molecule. The positive charge is preferably shielded, however, by substituents on the N or P atom which replace the acidic hydrogen atoms and which sterically shield the charge to disallow electrostatic binding to negatively charged species, such as cell membranes and proteins, to which binding of the sensitizer is undesirable. Thus, since the sensitizer will be bound primarily to target DNA/RNA, and not to cells or proteins, the likelihood of destruction of cells or proteins by the sensitizer upon irradiation is minimized.
> The psoralens (such as 8-MOP and AMT) must often be used in combination with a quencher (e.g. mannitol, vitamin E, etc.) to protect, repair or otherwise offset the deleterious effects of the sensitizer and light on cell membranes. The psoralen sensitizers herein do not accumulate in viral membranes and as a consequence do not require the presence of a quencher additive to the blood product."

Disregarding that Platz does not teach compounds of Applicants' claims, there would be no motivation to develop quenchers at all with the cationic compounds of Platz. With respect to Applicants' prior arguments, the Office Action indicates that "While the reason for contacting the claimed sample with the claimed compounds and claimed quencher may be slightly different than that disclosed by applicant, as applicant is surely aware, claimed subject matter must be held obvious if the prior art suggests its practice, even if the prior art motivation is different than applicant's". As discussed above and in the declaration of Dr. Wollowitz, Platz does not disclose all of the limitations to Applicants' claimed structure, therefore the claimed compounds are not disclosed by Platz.

> "The amine (or phosphine) of Platz, however, without other functional groups attached, is not inherently electrophilic, but is generally nucleophilic. Platz does not indicate any such functional groups...
> Further, there are no other moieties on the compounds described by Platz that are, or form, electrophilic groups that react covalently with nucleic acids." (Wollowitz declaration item 4)

The reason for contacting compounds disclosed in Platz with a quencher is significantly different from Applicants' reasons because Applicants' compounds are significantly different from any compounds disclosed by Platz. As discussed in the declaration, the covalent reaction of glutathione is well understood as a means to protect cells from damaging reaction of the nucleic acid with alkylators. This reactivity itself would suggest it would effectively quench not only unwanted side reactions but the desired activity of the alkylator on the nucleic acid of the pathogens. There is nothing in Platz that suggests otherwise and the fact that Platz uses quenching of free radicals in a pathogen inactivation system does not make it obvious to use the same quencher in Applicants' unrelated system.

> "The quenching of electrophiles by glutathione as it applies to Applicant's invention is neither described nor implied by Platz. Glutathione, and thiols in general, are known to react with electrophiles by a different mechanism than they react with singlet oxygen or reactive oxidative species. For example, the reaction of nucleophilic glutathione with electrophilic nucleic acid alkylators to protect cells occurs by a process in which the thiol group (RS-) covalently reacts with the alkylator [see, e.g. Bolton et al., Drug Metabolism and Disposition 21(6): 986-996, 1993]. The reaction of glutathione with singlet oxygen, other highly reactive oxygen species or free radicals involves the donation of an electron and/or a hydrogen atom to "quench" the reactive species, resulting in the formation of a thiol radical ($RS^{\cdot}$) which can then dimerize, be oxidized further or pull a hydrogen off another thiol in the medium. There is nothing in the disclosure of Platz to suggest that the reactivity of glutathione with an electrophilic nucleic acid alkylator is envisioned." (Wollowitz declaration item 6)

Thus, it is important that the motivation for adding quencher in Platz is different than the motivation for Applicants' addition of quencher, and it is because of this difference that Platz does not make Applicants' use of glutathione as a quencher obvious. Applicants respectfully request that this rejection be withdrawn.

Rejection under obviousness-type double patenting

Claims 1-20 are rejected under obviousness-type double patenting as being unpatentable over claims 20-35 of U.S. Patent 6,093,725 in view of U.S. Patent 5,418,130. For the reasons discussed above, in particular that Platz teaches away from using a quencher, Applicants feel that Platz would not motivate the artisan of ordinary skill to consider the general idea of an antioxidant quencher disclosed in Platz to be effective in Applicants' unrelated system. The consideration of Applicants' previous argument indicates that Applicants ignore the idea that the claims encompass a process resulting in free radical damage. Applicants' process involves the quenching of an electrophilic covalent reaction that is unrelated to a process involving free radicals as discussed in Platz. Whether there is free radical damage or not is irrelevant to Applicants' invention. Applicants believe that the present claims and those of 6,093,725 are patentably distinct and respectfully request that the obviousness-type double patenting rejection be withdrawn. Applicants have been requested to show common ownership of the present application and U.S. patent 6,093,725. While Applicants believe that this is not necessary, a declaration under 37 CFR 1.78(c) is submitted.

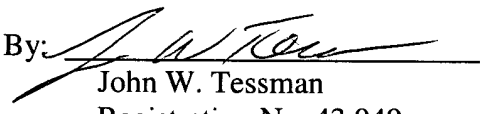
CONCLUSION

For the reasons set forth above, it is respectfully submitted that Applicant's claims are in condition for allowance and such allowance is earnestly solicited.

The Assistant Commissioner is hereby authorized to charge any additional fees associated with this petition or credit any overpayment to **Deposit Account No. 19-4315. A duplicate copy of this petition is enclosed for that purpose.**

Respectfully submitted
CERUS CORPORATION

Date: September 4, 2003

By: 

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